Remarks

Applicant thanks the Office for correcting the sequence listing and for restarting the period for responding to the Office Action.

Unexamined subject matter

Claims 1, 2, and 16-23 have been examined with respect to propylthiouracil as the elected species thyroid hormone-lowering agent. If the these claims are found allowable with respect to the elected species of propylthiouracil, Applicant respectfully requests that the patentability of claims 1, 16-23, and new claims 24 and 25 be considered with respect to the other species of thyroid hormone-lowering agent recited in claims 3-5. M.P.E.P. § 809.02(e).

The Amendments

Claim 1 is amended to recite that the amount of the administered thyroid hormone lowering agent "effective to decrease a level of a thyroid hormone in the mammal to a low normal level or to a below normal level." See Example 5, which teaches low normal and below normal levels of thyroid hormones in healer vs. non-healer mice.

New claim 24 is supported at page 3, lines 26-27: "Wounds whose healing can be increased according to the invention include, but are not limited to, ischemic infarcts . . . ." New claim 25 is supported *inter alia* by Examples 2, 3, 5, and 8, which teach detection of increased healing.

Neither the amendments nor the new claims add new matter. No new search is required.

The Rejection of Claims 1, 2, 16-19, 21, and 23 Under 35 U.S.C. § 102(b)

Claims 1, 2, 16-19, 21, and 23 stand rejected under 35 U.S.C. § 102(b) as anticipated by Corte *et al.*, *Gass. Med. Ital. Arch. Aci. Med. 152*, 149-53, 1993 ("Corte"). Applicant respectfully traverses the rejection.

A printed publication that antedates an invention under 35 U.S.C. § 102 must disclose each element of the invention. *Kalman v. Kimberly-Clark Corp.*, 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Corte does not meet this standard.

Corte is cited as teaching increased healing of an ischemic heart in a human patient by administering propylthiouracil after ischemic injury occurred. Office Action at page 3. Corte, however, does not teach all the elements of amended independent claim 1. Independent claim 1 has been amended to recite that the amount of the administered thyroid hormone lowering agent "effective to decrease a level of a thyroid hormone in the mammal to a low normal level or to a below normal level." Corte does not teach this element of claim 1.

The human patient described in Corte was "a patient affected with hyperthroidism, who during a thyrotoxic crisis developed acute myocardial ischemia . . . ." Page 3, third paragraph of the translation. Upon administration to the hospital her T3 level was 400 ng/dL and her T4 level was 20 μg/dL. Page 6, first paragraph. These TH levels are above the normal range for humans, which is 100-200 ng/dL for T3 and 5-12 μg/dL for T4. See Attachment 1. The patient was treated with propylthiouracil and propanolol.

After propylthiouracil treatment, this patient's thyroid hormone levels were not decreased to a low normal level or to a below normal level, as recited in amended claim 1. After three

months of propylthiouracil therapy, the patient's T3 level was 200 ng/dL and her T4 level was 12 μg/dL. Page 7, third full paragraph. These levels are each at the high end of the normal range. The specification teaches that low normal or below normal TH levels are associated with wound healing. See Example 4. It is, therefore, unlikely that the propylthiouracil treatment increased healing of the patient's ischemic damage. In fact, Corte teaches that "[t]he rapidity of the regression of electrocardiographic signs of ischemia and the clinical improvement are to be attributed to the action of the Propanolol, given that Propylthiouracil needs a greater lapse of time to perform its effects.". Page 9, second full paragraph.

Corte does not teach that administration of propylthiouracil to the patient was "effective to decrease a level of a thyroid hormone in the mammal to a low normal level or to a below normal level," as recited in amended claim 1. Thus, Corte does not teach each element of amended claim 1 and therefore does not anticipate claims 1, 2, 16-19, 21, or 23. Because new claims 24 and 25 depend from claim 1, Corte also does not anticipate these claims.

Applicant respectfully requests withdrawal of the rejection.

<u>The Rejection of Claims 1, 2, 17-20, 22, and 23 Under 35 U.S.C. § 102(b)</u>

Claims 1, 2, 17-20, 22, and 23 stand rejected under 35 U.S.C. § 102(b) as anticipated by Alpert *et al.*, *Eur. Heart J. 5*, 3-11, 1984 ("Alpert"). Applicant respectfully traverses the rejection.

Alpert is cited as teaching administration of propylthiouracil to a WKY rat prior to and concomitant with wounding the heart by removing myofibrils for *in vitro* experiments. Office

Action at page 4. The Office Action acknowledges that Alpert does not teach that levels of T3 or T4 are lowered or that reepithelialization occurs, but asserts that these results of propylthiouracil administration are inherent in Alpert's disclosure. Office Action at page 4.

To establish inherency, extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1759 (Fed. Cir. 1991) (emphasis added). Alpert does not meet this standard. Alpert discloses *in vitro* experiments carried out on myofibrils removed from either control rats or rats treated with propylthiouracil. Page 4, col. 2. Rather than healing from the removal of myofibrils, it is evident that neither group of rats survived. Table 1 of Alpert discloses the body and heart weights of the two groups of rats. See page 6, col. 2. To weigh a heart, it must be removed from the body; it is self-evident that a rat would not survive removal of its heart. Thus, no healing of a heart wound in a propylthiouracil-treated mammal inherently occurred at all in Alpert's rats, much less increased healing.

Alpert does not explicitly or inherently disclose the invention of claims 1, 2, 17-20, 22, or 23, or of new dependent claim 24. New claim 25 recites a step of detecting increased healing of a heart wound. Alpert neither explicitly nor inherently discloses this step.

Applicant respectfully requests withdrawal of the rejection.

Respectfully submitted,

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Date: April 7, 2003

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Attachment 1

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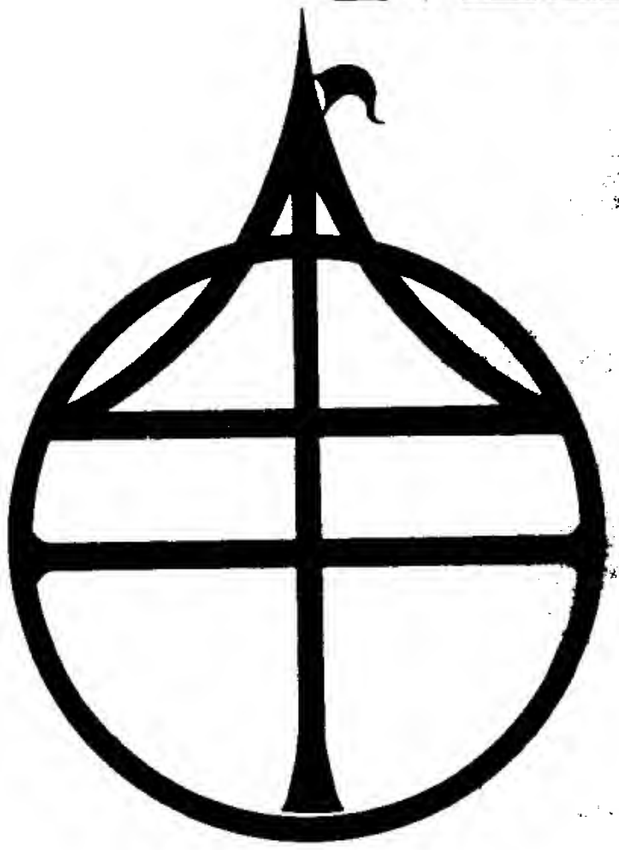

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W.B. SAUNDERS COMPANY

A Division of Harcourt Brace & Company

PHILADELPHIA • LONDON • TORONTO • MONTREAL • SYDNEY • TOKYO

W. B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, PA 19106

Library of Congress Cataloging-in-Publication Data

Cecil textbook of medicine / edited by J. Claude Bennett, Fred Plum.—20th ed.

p. cm.

Includes bibliographical references and index.

ISBN 0-7216-3561-X (single v.).—ISBN 0-7216-3574-1 (v. 1).—ISBN 0-7216-3575-X (v. 2).—ISBN 0-7216-3573-3 (set)

1. Internal medicine. I. Cecil, Russell L. (Russell La Fayette), 1881-1965. II. Bennett, J. Claude. III. Plum, Fred, IV. Title: Textbook of medicine.
[DNLM: 1. Medicine. WB 100 C3888 1996]

RC46.C423 1996
616—dc20

DNLM/DLC 94-43773

ISBN 0-7216-3574-1 Volume 1
ISBN 0-7216-3575-X Volume 2
ISBN 0-7216-3573-3 Set (Vols 1 & 2)
ISBN 0-7216-3561-X Single volume

CECIL TEXTBOOK OF MEDICINE

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2

CLINICAL CHEMISTRY, TOXICOLOGY, SEROLOGY *Continued*

Test	Specimen	Reference Interval (Conventional Units)	Reference Interval (International Units)
Sodium	Serum or plasma (heparin)	136–146 mEq/L	136–146 mmol/L
	Urine, 24-h	40–220 mEq/d	40–220 mmol/d
Specific gravity	Urine, random		1.002–1.030
	Urine, 24-h	[illegible] total	1.015–1.025
Testosterone, free	Serum	M: 52–280 pg/mL 1.5–3.2 F: 1.6–6.3 pg/mL 0.8–1.4	180.4–971.6 pmol/fraction of total L 5.6–21.9 pmol/L 0.015–0.032 0.008–0.014
Testosterone, total	Serum	M: 300–1000 F: 20–75	10.4–34.7 nmol/L 0.69–2.6 nmol/L
	Urine	20–50 y: M: 50–175 µg/d F: 2–12 µg/d >50 y: M: 30–60 µg/d F: 2–8 µg/d	 173–470 nmol/d 7–42 nmol/d 139–210 nmol/d 7–28 nmol/d
Thiamine (see Vitamin B_1)	Serum		
Thyroglobulin (Tg)	Serum	3–42 ng/mL	3–42 µg/L
Thyroglobulin antibodies	Serum		<1:10
Thyroid microsomal antibodies	Serum		Nondetectable (hemagglutination) or <1:10 (IFA)
Thyrotropin (hTSH)	Serum or plasma	2–10 µU/mL	2–10 mU/L
Thyrotropin-releasing hormone	Plasma	5–60 pg/mL	5–60 ng/L
Thyroxine, free (FT_4)	Serum	0.8–2.4 ng/dL	10–31 pmol/L
Thyroxine (T_4), total	Serum	5–12 µg/dL	65–155 nmol/L
		>60 y, M: 5.0–10.0 µg/dL	65–129 nmol/L
		F: 5.5–10.5 µg/dL	71–135 nmol/L
Thyroxine-binding globulin (TBG)	Serum	15.0–34.0 µg/mL	15.0–34.0 mg/L
Thyroxine index, free (see Free thyroxine index)			
		T_4 (µg/dL)/TBG (µg/mL)	T_4 (nmol/L)/TBG (mg/L)
Transcortin	Serum	M: 18.8–25.2 mg/L	323–433 nmol/L
		F: 14.9–22.9 mg/L	256–393 nmol/L
Transferrin	Serum	200–400 mg/dL	2.0–4.0 g/L
		>60 y: 180–380 mg/dL	1.80–3.80 g/L
Transthyretin (prealbumin)	Serum	10–40 mg/dL	100–400 mg/L
Triglycerides (TG)	Serum, after ≥12-hr fast	Recommended: M: 40–160 mg/dL F: 35–135 mg/dL	0.45–1.81 mmol/L 0.40–1.52 mmol/L
Tri-iodothyronine, free	Serum	260–480 pg/dL	4.0–7.4 pmol/L
Tri-iodothyronine, total (T_3)	Serum	100–200 ng/dL	1.54–3.08 mmol/L
Tri-iodothyronine resin uptake test (T_3RU)	Serum	24–34%	24–34 AU (arbitrary units)
Urea nitrogen	Serum or plasma	7–18 mg/dL	2.5–6.4 mmol/L
	Urine	12–20 g/d	0.43–0.71 mol/d
Urea nitrogen/creatinine ratio	Serum		12/1–20/1
Uric acid (uricase)	Serum	M: 3.5–7.2 mg/dL	0.21–0.42 mmol/L
		F: 2.6–6.0 mg/dL	0.15–0.35 mmol/L
	Urine, 24-h	250–750 mg/d	1.48–4.43 mmol/d
Urinary sediment (see Sediment)			
Urobilinogen	Urine, 2-h	0.1–0.8 EU	0.1–0.8 U
	Urine, 24-h	0.5–4.0 EU	0.5–4.0 U
	Feces	75–275 EU/100 g	750–2750 U/kg
		75–400 EU/d	75–400 U/d
		40–280 mg/d	67–473 µmol/d
Uroporphyrin	Urine, 24-h	<50 µg/d	<60 nmol/d
	Feces, 24-h specimen	10–40 µg/d	12–48 nmol/d
	Erythrocytes (heparin or EDTA)		Negative
Vanillylmandelic acid (VMA)	Urine, 24-h	2–7 mg/d	10.1–35.4 µmol/d
Viscosity	Serum		1.10–1.22 centipoise
Vitamin A	Serum	30–80 µg/dL	1.05–2.8 µmol/L
Vitamin B_1 (Thiamine)	Serum	0–2 µg/dL	0–75 nmol/L
Vitamin B_2 (Riboflavin)	Serum	4–24 µg/dL	106–638 nmol/L
Vitamin B_6	Plasma (EDTA)	5–30 ng/mL	20–121 nmol/L
Vitamin B_{12}	Serum	100–700 pg/mL	74–516 pmol/L
Vitamin C	Plasma (oxalate, heparin, or EDTA)	0.5–1.5 mg/dL	28–85 µmol/L
Vitamin D_3, 1,25-dihydroxy	Serum	25–45 pg/mL	60–108 pmol/L
Vitamin D_3, 25-hydroxy	Plasma (heparin)	Summer: 15–80 ng/mL	37.4–200 nmol/L
		Winter: 14–42 ng/mL	34.9–105 nmol/L
Vitamin E	Serum	5.0–18.0 µg/mL	12–42 µmol/L
Zinc	Serum	70–150 µg/dL	10.7–22.9 µmol/L